Allergic rhinitis: To sneeze or to wheeze. Pollen is the question, what is the answer?

Bjorn Martin, BPharm, Academic intern
Alexander Wehmeyer, BPharm, Academic intern
Edward Upton, BPharm MPharm, Lecturer
School of Pharmacy, University of the Western Cape
Correspondence to: Edward Upton, e-mail: eupton@uwc.ac.za

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Abstract

Allergic rhinitis, also known colloquially as hay fever, is the most common among the allergic diseases. Recent literature reports that it affects up to a tenth of the world population. Atopic diseases have a particularly high prevalence in young children which is often attributed to their immature immune systems. Traditionally, atopic diseases have plagued industrialised countries, but the burden has recently extended its reach to developing countries. Over the past few decades, there has been a marked increase in all allergy-related diseases. Supported by the advent of the *Atopic March*, research has been primarily directed at understanding the aetiology and pathophysiology associated with diseases stemming from atopy. In this article, we review current treatments available in South Africa and explain the pathophysiology of allergic rhinitis.

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Introduction

Atopy (Greek: atopia, out of place) denotes an inherited, genetic predisposition or familial response resulting in the elevated expression of immunoglobulin E (IgE) antibodies.[1] It is estimated that some form of an atopic disease will affect one out of every five people during the course of their life.[1-4] In Africa's adolescent population, a marked rise in the symptoms of allergic rhinitis (AR), atopic dermatitis as well as asthma has been observed over the past decade.[5-7] This apparent surge of allergic diseases has been associated with increased global urbanisation.[6] In South African adolescents, an increase in urbanisation has seen the prevalence of eczema increase from 11.8% in 1995 to 19.4% in 2001.[8]

The risk of developing an atopic disease is largely dependent on both environmental and genetic aspects related to the individual.[1,9] Individuals who are typically termed 'atopic' possess a genetic predisposition to developing allergy-related conditions.[10]

Allergic rhinitis

IgE-mediated type 1 hypersensitivity reactions are the hallmark of allergic rhinitis (AR). This reaction is an elevated immune response which is triggered by the relatively minute inhalation of common environmental proteins such as pollen and house dust mites.[7] Although AR is usually characterised by a nasal discharge, sneezing and sinal congestion, it initially presents in the form of asymptomatic sensitisation. This individual, with confirmed allergic sensitisation to one or more allergens, does not exhibit clinical allergy upon his/her first exposure to an allergen.[11] Only after initial exposure to an allergen do they become sensitised toward it.[12] After sensitisation, re-exposure will typically result in an exacerbation of AR.

AR stems from a genetic predispositioning as well as early childhood environmental factors. Often those not exposed to enough bacteria at a young age will develop an atopic condition. Environmental and genetic factors lead to an imbalance between T-helper 1 (T_h1) and T-helper 2 (T_h2) cellular responses. This imbalance between T_h1 and T_h2 cellular responses is at the centre of the pathophysiology relating to allergic diseases.[13] Antibiotic use in early infancy is proven to cause severe disturbances in bowel microbiota and use of antibiotics during early childhood developmental phases has been positively correlated with an increased risk toward the development of atopy.[14-16] These findings have created a strong link between AR and the hygiene hypothesis.

Pathophysiology

The pathophysiology of atopic conditions is a series of complex interactions between an individual's immune system and an allergen. Although atopic diseases such as asthma, atopic dermatitis and AR present very differently, they originate from similar immunological abnormalities. The distinguishing factor among these diseases is the presentation of the clinical symptoms. The same allergen can easily cause three different allergic responses for three different people. One person may suffer an asthma attack upon inhaling pollen. The other may have purulent nasal discharge, nasal congestion and watery eyes.[17-19]

Individuals who are genetically predisposed will have an imbalance between T_h1 and T_h2 cellular responses, with a bias

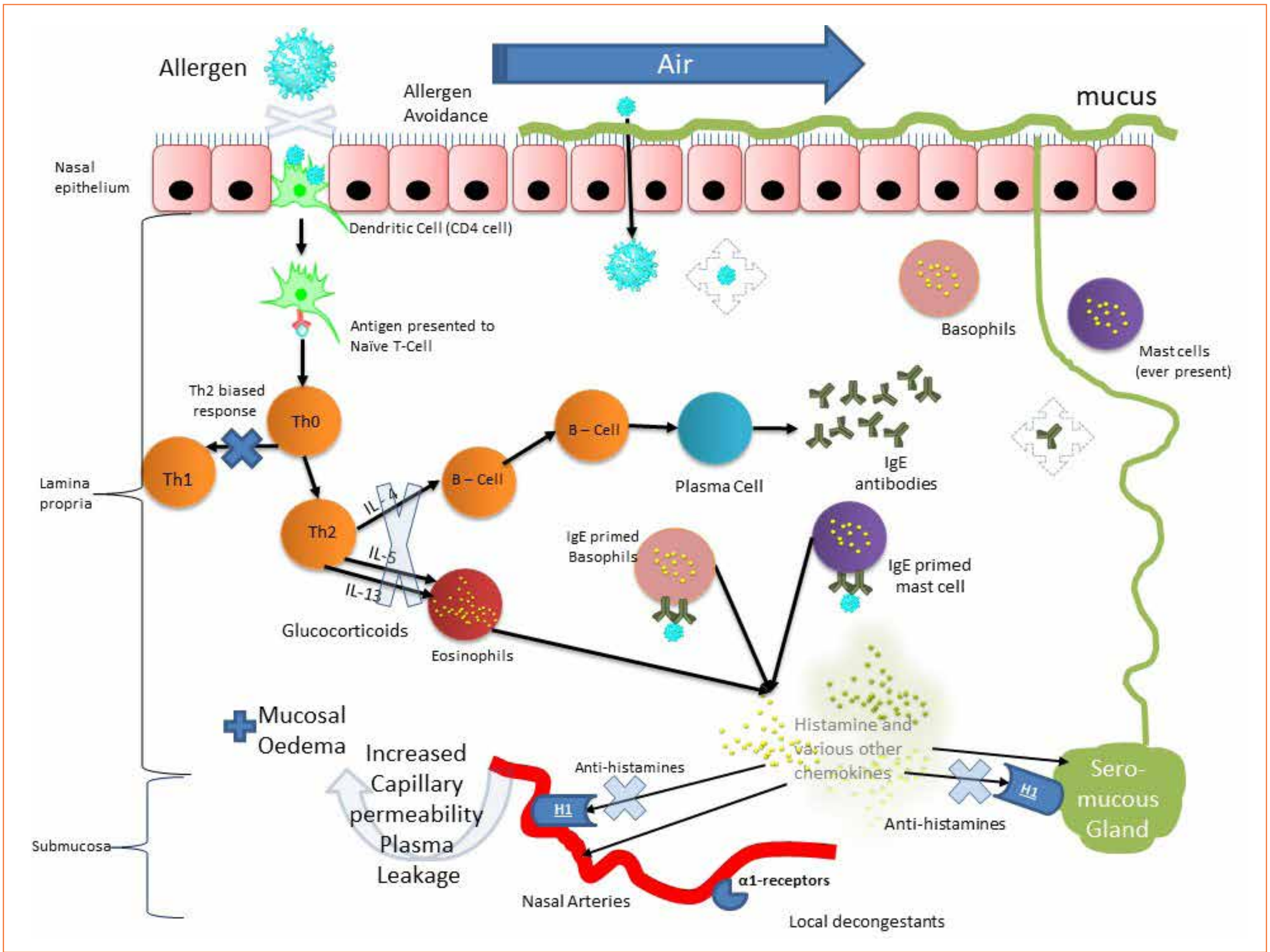

Figure 1. A graphic representation of the pathophysiological processes in AR, including the mechanism behind the different treatment options indicated by the transparent X, which indicates a blockage or suppression of cascading events. Allergens are inhaled. They penetrate through the epithelial layer and are detected by the dendritic cells. Dendritic cells activate T_h2 cellular processes. IL4, -5 and -13 are released. IL-4 stimulates B-cells to transform into IgE producing plasma cells. IgE freely distributes through the lamina propria and primes mast cells and basophils. Primed mast cells and basophils degranulate upon IgE binding to an allergen and release histamine, leukotrienes, prostaglandins and various other cytokines. These cytokines then cause vasodilation of the nasal arteries and increased capillary permeability of the sinal capillaries. Increased permeability leads to increased plasma leakage, sinal oedema and a nasal discharge. These cytokines also cause sero-mucous glands to increase mucus production. Cytokines also attract various other pro-inflammatory immune cells. Eosinophils that are activated by IL-5 and IL-13 also release similar cytokines to basophils and mast cells.[20-22]

toward the T_h2 cellular response. The cascading immune response usually commences with an allergen being identified by an antigen-presenting cell such as a dendritic cell. T_h2 cells start to proliferate from naïve T_h0 cells presented with the allergen-specific antigen.[17-21]

T_h2 cellular response triggers the release of pro-inflammatory cytokines, IL-4, IL-5 and IL-13, which have been identified as the main driving forces behind AR pathophysiology. The release of these cytokines leads to transformation of beta-cells to IgE-producing plasma cells and the attraction of eosinophils. IgE produced by plasma cells then binds to mast cells and eosinophils via the FcεRI receptor. This leads to the release of histamine, prostaglandins, leukotrienes and other cytokines. Some eosinophilic-derived cytokines have also been reported to cause mucosal remodelling in atopic rhinitis, atopic dermatitis and atopic asthma. Depending on the atopic disease, various other cytokines are also involved in the pathology of atopic diseases.[17-19] These released cytokines and histamine then increase capillary permeability, leading to plasma leakage from the nasal capillaries. They also stimulate sero-mucous glands to produce more mucus. These two effects are the main cause for nasal discharge and congestion.[20-22]

Approach to therapy

Three fundamental approaches in the management of AR are in effect, which are non-pharmacological management, standard pharmacotherapy and immunotherapy. Non-pharmacological management possesses the ability to lessen or abolish symptoms of AR as well as the number of pharmacological therapies required for symptom alleviation and management.[23,24]

Non-pharmacological treatment

Allergen avoidance is a practical and simplistic form of non-pharmacological management of AR. The initial step in this method includes identification of suspected allergens through allergy testing or through direct identification by patients. Following this step, patients should take active measures to avoid or reduce exposure to pre-identified triggers. Allergen avoidance should be incorporated as an essential component in the overall therapeutic management of patients suffering from AR.[23,25]

Pharmacotherapeutic considerations should examine efficacy, safety, cost as well as patient preference aspects of available therapies. Treatment is typically administered via the oral or intranasal routes.[23,26]

Pharmacological treatment

AR management strategies usually consist of local decongestants, antihistamines, and corticosteroids, which are primarily utilised as nasal decongestants to effectively reduce nasal obstruction. These active pharmaceutical ingredients (APIs) may be delivered via various administration routes (e.g. pulmonary, oral) and the resultant variety of dosage forms create a pool of medicinal options available for tailored pharmaceutical regimens. As stated in ARIA (Allergic Rhinitis and its Impacts on Asthma) guidelines, pharmacological treatment must be individualised, with consideration of factors such as severity of disease, safety, cost-effectiveness of medications, patient's preference, likely adherence to recommendations, severity and control of the disease, and the presence of comorbidities and polypharmacy.[27] Although antihistamines and corticosteroids are the mainstay of treatment for AR, local and systemic adverse effects limit their period of use, even if only for seasonal AR.[28]

Locally-acting decongestants

These agents are characterised by adrenergic medications, such as phenylephrine, xylometazoline and oxymetazoline, which produce vasoconstriction through the stimulation of α1-adrenergic receptors. The resultant effect is a reduction in mucosal oedema as well as a local dilatory effect. However, it should be noted that the effect of these agents is only evident for a limited period of time.[29,30]

The greatest issue associated with the use of these agents, is the risk of rebound nasal congestion or rebound rhinitis following prolonged use. These effects occur via downregulation of α-receptors and are characterised by nasal hyper-reactivity and congestion. These negative effects may become apparent following continuous use of these agents for periods lasting longer than three consecutive days. Other commonly associated adverse effects include nasal burning and dryness.[23,31,32]

Local corticosteroids

Glucocorticosteroids modify protein synthesis through regulating transcription and indirectly by modifying the activity or half-life of transcription factors and mRNA. These result in the suppression of T_h2 cellular activity, thus various cytokines involved in the pathophysiology of AR are no longer synthesised and released, including IL-4, IL-5 and IL-13 which have been identified in the pathophysiology of AR.[22] The following intranasal corticosteroids are currently available: beclomethasone, budesonide, fluticasone, mometasone, triamcinolone and ciclesonide. Intranasal administration of the newer agents, namely mometasone, fluticasone, and ciclesonide, will result in minimal systemic effects.[33] The most frequent local side-effects experienced with the intranasal corticosteroids include dryness, stinging, burning, and epistaxis. Chronic use of topical corticosteroids may lead to atrophy of the nasal mucosa.[33,34] Although the use of corticosteroids constitutes the most effective treatment for the inflammation experienced in AR, when these agents are used for seasonal allergic conjunctivitis, pulse dosing should rather be utilised, for as short a treatment duration as possible.[35]

Histamine-1-(H_1)-antihistamines

The overall goal of H_1-antihistamine therapy is to alleviate current symptoms associated with allergic diseases and prevent long-term complications as well as symptoms.[23,36] Therefore these agents typically see use in the treatment of allergy-related diseases, such as AR, allergic conjunctivitis and urticaria, where they are considered standard therapy.[23,40] However, they do not form part of the mainstay of treatment in cases of severe hypersensitivity reactions, such as anaphylaxis and angioedema that constitute emergency situations. This may be attributed to antihistamines not relieving serious associated complications such as airway obstruction, shock and hypotension. The pharmacological mechanism by which these agents act is primarily through the antagonisation of H_1-receptors on various target tissues. This resultant effect will be a lowered histamine-mediated immune response.[23]

H_1-antihistamines may be sub-divided into two differing classes, which are the first-generation H_1-antihistamines and the second-generation H_1-antihistamines. The first-generation H_1-antihistamines are known as the older-type agents that are multi-potent antagonists. These agents cross the blood-brain barrier to a significant degree, which precipitates their commonly associated sedative-like effects. In contrast, the second-generation H_1-antihistamines possess a significantly limited ability or no ability to cross the blood-brain barrier and thus are noted to be non-sedating. These agents are also noted to be newer and are associated with selective H_1-receptor activity. Various formulations of H_1-antihistamines are available, such as oral, parenteral as well as topical preparations, which includes intranasal and ophthalmic agents.[36-38] Examples and pharmacological characteristics of H_1-antihistamines are presented in Table I.

- *First-generation H_1-antihistamines*
  In consideration of the fact that these agents possess substantial blood-brain barrier permeability and their multi-potent receptor-antagonism in numerous receptor systems, it may be understood that their chemical structures permit non-selective antagonism. Their non-selective antagonism is inclusive of anti-muscarinic, anti-serotonergic, anti-histaminergic and α1-adrenergic blockade effects.[36,39,40] Therefore adverse effects such as sedation, fatigue, headache, drowsiness and xerostomia (dry

Table I. Pharmacological characteristics of typically used H1-antihistamines in allergies[30,36 and Criado et al, 2010]

Antihistamine	Onset of action	Drug interactions	Associated half-life
First-generation antihistamines			
Chlorpheniramine maleate (e.g. Allergex®; Rhineton®)	30 to 60 minutes	Alcohol, central nervous system depressants, tricyclic antidepressants Anticholinergic agents, drugs affecting CYP2D6 enzymes	12 to 15 hours
Hydroxyzine HCl* (e.g. Aterax®)	2 hours		16 to 24 hours
Prometazine HCl (e.g. Phenergan®)	20 minutes		10 to 14 hours
Second generation			
Cetirizine HCl (e.g. Allecet®; Texa®)	1 to 3 hours	Unlikely	10 hours
Desloratadine (e.g. Deselex®; Dazit®, Pollentyme ND®)	2 hours	Unlikely	27 hours
Ebastine (e.g. Kestine®)	2 hours	Potential	15 to 19 hours
Fexofenadine HCl** (e.g. Telfast®; Tellerge®)	2 hours	Unlikely	14 hours
Levocetirizine HCl (e.g. Xyzal®; Allerway 5; Levogex®)		Unlikely	8 hours
Loratadine (e.g. Clarityne®, Pollentyme®)	1 to 3 hours	Unlikely	12 to 15 hours
Mizolastine (e.g. Mizollen®)	1 hour	Potential	12.9 hours

*HCl – Hydrochloride. **Fexofenadine HCl has replaced terfenadine due to its severe cardiac adverse effects.

mouth) are prevalent in patients who utilise these agents.[36,41] As such, Kulthanan, et al noted in their clinical practice guideline for the diagnosis and management of uticaria that because of the associated adverse effects of first-generation H_1-antihistamines their use should be avoided in patients with contraindications, such as glaucoma and asthma, as well as in the elderly.[37]

Further, few prospective clinical pharmacology trials exist where these older-type H_1-antihistamines were studied in special populations, such as paediatric and geriatric populations nor patients with renal or hepatic impairment. In addition, studies highlighting the interactions of these agents with medications, food and herbal agents are evident.[36,42]

In a randomised controlled trial, conducted by Staevska, et al, it was concluded that the practice of adding a first-generation H_1-antihistamine for its sedative effects at night was not supported. In addition, the trial also noted that their findings corresponded to various uticaria guidelines, which recommended only a second-generation H_1-antihistamine without the addition of a first-generation agent in the treatment of uticaria.[43]

It should be noted that the multi-potency of their receptor-blocking capabilities has enabled their use in several varying conditions and has thus broadened their indications. These indications include[30,36,39]:

- *Insomnia:* Agents such as diphenhydramine and promethazine are noted to be effective for the short-term relief of insomnia through their sedative properties.
- *Allergy-related conditions:* It has been established that chlorpheniramine exhibits fewer sedative properties and is thus a better agent for the management of allergy-related conditions.
- *Anti-emesis:* Agents, such as cyclizine, may be useful in the treatment of vertigo. However, they are also indicated in the treatment of post-operative nausea and vomiting.
- *Second-generation H_1-antihistamines*

  This class of newer, non-sedating H_1-antihistamines is noted for being long-acting in comparison to first-generation H_1-antihistamines. In addition to their lack of central nervous system penetration, they are devoid of any significant anti-emetic activity and anticholinergic-associated adverse effects.[37,40] For the majority of these agents, their pharmacokinetics have been comprehensively studied in paediatric and geriatric patients. In addition, these effects have also been investigated in patient populations who suffer from renal and hepatic dysfunction.[30,36,42] However, many of these agents are metabolised by the cytochrome 450 enzyme during first pass hepatic metabolism and are therefore not recommended for patients with liver impairment.[40] Their associated interactions with other medications, food and herbal products are well characterised, however, they are known to rarely be clinically pertinent.[36]

Treatment efficiency of several second-generation H_1-antihistamines, which include desloratadine and levocetirizine, has been shown to be enhanced with a 4-fold dose increase without increasing the risk of associated adverse effects.[44,43] Synonymously, the results of a randomised controlled trial revealed that a 240 mg daily dose of fexofenadine reduced pruritus on the visual analogue scale significantly when compared to a 120 mg daily dose.[45]

Non-sedating antihistamines are proposed to be first-line therapy with special consideration for use in patients whose occupations and/or interests necessitate a lack of sedation.

These include patients who are heavy machinery operators, delivery or truck drivers and students. This is synonymous with the recommendation for the phasing out of sedating-antihistamine use.[37,41]

Conclusion

Various medications are available to treat AR and are generally well tolerated. Nonpharmacological management, such as allergen avoidance, should form the mainstay of therapy. Antihistamines should be recommended for patients presenting with mild, intermittent symptoms related to AR. Evidence suggests that second-generation antihistamines should be used in place of first-generation antihistamines due to their more favourable adverse effect profiles. Pharmacists play an important role in AR treatment through aiding in product selection on the basis of patient-specific symptoms and patient-individual factors, counselling around appropriate use of the selected product as well as patient referral where necessary.

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